DETAILED ACTION

Claim amendments filed on 06/03/2011 have been entered.

Claims 16-18 are cancelled. Claim 1 is amended. Claim 31 is newly added. Claims 1-15 and 19-31 are pending.

This application 10/598,356 is a 371 of PCT/US2005/006108 filed on 02/24/2005 which claims benefit of 60/547,145 filed on 02/24/2004.

Election/Restriction

Amended claim 1 filed on 06/03/2011 reads as follows: A method of treating a patient with recurrent cancer comprising: (a) selecting a recurrent cancer patient previously treated with surgery or first radio- or chemotherapy prior to such recurrence; (b) administering to said patient an expression construct comprising a nucleic acid segment encoding p53, said segment under the control of a promoter active in a cancer cell of said subject, said expression construct expressing p53 in said cancer cell; and (c) subsequent to step (b), administering to said patient a second radio- or chemotherapy, wherein the time period between administration of said second radio- or chemotherapy relative to the administration of said expression construct is at least 7 days; whereby said expression construct sensitizes said cancer cell to said second radio- or chemotherapy, thereby treating said cancer.

Newly added claim 31 filed on 06/03/2011 reads as follows: A method of treating a patient with recurrent cancer, the method comprising administering p53 therapy to the patient, followed by administering a first post-therapy treatment with radio- or chemotherapy at least 7 days thereafter.

The Examiner notes that newly added independent claim 31 filed on 06/03/2011 is a genus claim that encompasses the scope of independent claim 1. In this regard, it is worth noting that, for instance, the breadth of "p53 therapy" recited in newly claim 31 encompasses any therapy directly or indirectly linked to the biological function of p53 at nucleic acid and/or protein level(s), which is much broader than "a nucleic acid segment encoding p53" recited in

claim 1. It is emphasized that the full breadth of newly claim 31 also encompasses the non-elected Groups I, II, and IV-VI inventions (See Restriction/Election mailed on 12/09/2011). In other words, newly added claim 31 is assigned to existing Groups I-VI inventions documented Restriction/Election mailed on 12/09/2011. The embodiments currently unspecified and encompassed by generic independent claim 31 that do not belong to existing Groups I-VI inventions may be subject to further Restriction/Election in future prosecution.

Independent claim 31 is examined to the extent of elected Group III invention (See Restriction/Election mailed on 12/09/2011), claims 1, 3-26, 29, and 30, drawn to a method of treating a patient with recurrent cancer comprising: (a) selecting a recurrent cancer patient previously treated with a *radiotherapy* prior to such recurrence; (b) administering to said patient an expression construct comprising a nucleic acid segment encoding p53, said segment under the control of a promoter active in a cancer cell of said subject, said expression construct expressing p53 in said cancer cell; and (c) subsequent to step (b), administering to said patient a *chemotherapy*, wherein the time period between administration of said chemotherapy relative to the administration of said expression construct is at least 7 days; whereby said expression construct sensitizes said cancer cell to said chemotherapy, thereby treating said cancer (See amended claim 1 filed on 06/03/2011 in the context of elected Group III invention).

For the clarity of record, the following statements documented on pages 2-3 of Non-Final office action mailed on 12/09/2010 are reiterated below: In response to requirement for election of species, Applicant elected the following species elections without traverse: **(i)** carboplatin (recited in claim 5), **(ii)** x-rays (recited in claim 7), **(iii)** head & neck cancer (recite din claim 8), **(iv)** an adenoviral construct (recited in claim 10), **(v)** viral (recited in claim 9), (vi) replication defective (recited in claim 12), **(vii)** CMV IE promoter (recited in claim 15), **(viii)** about 14 (recited in claim 20), **(ix)** intratumoral (recited in claim 30), in the reply filed on 10/07/2010 is acknowledged. Applicant states that Applicants have therefore withdrawn claims 11, 13, 14, 16-19 and 21-24 as drawn to non-elected inventions, subject to rejoinder.

Upon searches and further consideration, **(i)** listed above the species election between "carboplatin" and "cisplatin" recited in claim 5 is *withdrawn*; and **(iii)** listed above the species election between "head and neck cancer" and "lung cancer" recited in claim 8 is *withdrawn*.

Claims 1-15 and 19-**31** are pending. Claims 2, 11, 13, 14, 19, 21-24, 27, and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1, 3-10, 12, 15, 20, 25, 26, 29, 30 and **31** are currently under examination (i) to the extent of elected Group III invention and (ii) to the extent of elected species, as stated above.

Claim Objections

1. Claim 1 and its dependent claims 3-10, 12, 15, 20, 25-26, 29 and 30, and independent claim **31** remain/are objected to for being drawn to a non-elected invention. Specifically, Applicants have elected Group III, claims 1, 3-26, 29, 30, and independent claim 31, drawn to a method of treating a patient with recurrent cancer comprising: (a) selecting a recurrent cancer patient previously treated with a *radiotherapy* prior to such recurrence; and (ii) recurrence of cancer subsequent to said treatment; (b) administering to said patient an expression construct comprising a nucleic acid segment encoding p53, said segment under the control of a promoter active in a cancer cell of said subject, said expression construct expressing p53 in said cancer cell; and (c) subsequent to step (b), administering to said patient a *chemotherapy*, wherein the time period between administration of said *chemotherapy* relative to the administration of said expression construct is at least 7 days; whereby said expression construct sensitizes said cancer cell to said *chemotherapy*, thereby treating said cancer (See amended claim 1 filed on 06/03/2011 in the context of elected Group III invention); and as such, claim 1 and dependent

claims 3-10, 12, 15, 20, 25-26, 29 and 30, and independent claim 31 are examined only to the extent that they read on the limitation "selecting a recurrent cancer patient previously treated with a *radiotherapy* prior to such recurrence" and the limitation "administering to said patient a *chemotherapy*, wherein the time period between administration of said *chemotherapy* relative to the administration of said expression construct is at least 7 days; whereby said expression construct sensitizes said cancer cell to said *chemotherapy"* recited in claim 1.

Applicants are required to delete the non-elected subject matter from the instant claims [i.e. non-elected subject matter being surgery and chemotherapy recited in step (a) of claim 1, and radiotherapy recited in step (c) of claim 1; and amending claims 3, 4, and 6 to be directed to first treatment being radiotherapy and second treatment being chemotherapy; and "followed by administering a first post-therapy with radiotherapy recited in line 3 of newly added claim 31 filed on 06/03/2011].

Applicant's arguments

Applicants state that all of the claims that read only on non-elected inventions have been withdrawn, subject to rejoinder. To the extent the remaining claims read on a non-elected invention, such claims should be considered linking claims which claims are not subject to withdrawal. See MPEP 809 ("The linking claims must be examined with, and thus are considered part of, the invention elected."). Thus, maintaining the linking claims in the case is appropriate.

Response to Applicant's arguments

The Examiner maintains the position that surgery, radiotherapy, and chemotherapy recited in steps (a) and (c) of claim 1 are patentably distinct treatments of a given cancer of interest. A format of a generic claim (or linking claim for a US case) that recites multiple distinct inventions in one independent claim does not negate the presence of multiple distinct

inventions encompassed by the claim. In other words, it is the claimed subject matters, not the format of claim itself, that direct the Restriction/Election practice. In this regard, it is noted that Applicant elected Group III invention *without traverse* in the reply filed on 07/06/2010. Furthermore, it is worth noting that "linking claim" is not germane to PCT lack of unity practice.

2. Claims 5 and 31 are objected to because of the following informalities: (i) The chemotherapy drug "carboplatinum" recited in claim 5 should read as "carboplatin". This is based on Applicant's election of species filed on 10/07/2010, and the spelling of "carboplatin" is consistent with the disclosure by Staar et al. cited in the 103 rejection. (ii) The last word "therafter" recited in claim 31 should read as "ther**e**after". Appropriate correction is required.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 3-10, 12, 15, 20, 25, 26 and 29-**31** remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over **Roth et al.** (US Patent 6,069,134, issued 05/30/2000) in view of **Roth et al.** (Roth et al., Retrovirus-mediated wild-type p53 gene transfer to tumors of patients with lung cancer, *Nat. Med.* 2(9):985-991, 1996; this reference has been cited as reference C10 in the IDS filed by Applicant on 02/23/2007), and **Staar et al.** (Staar et al., Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous

chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer, *Int J Radiat Oncol Biol Phys* 51(2):569, 2001). *It is noted that the inclusion of claim 31 in this maintained rejection is necessitated by claim amendments filed on 06/03/2011 adding new claim 31.*

Claims 1, 3, 4, and 6 are directed to a method of treating a patient with recurrent cancer comprising: (a) selecting a recurrent cancer patient previously treated with a *radiotherapy* prior to such recurrence; (b) administering to said patient an expression construct comprising a nucleic acid segment encoding p53, said segment under the control of a promoter active in a cancer cell of said subject, said expression construct expressing p53 in said cancer cell; and (c) subsequent to step (b), administering to said patient a *chemotherapy*, wherein the time period between administration of said chemotherapy relative to the administration of said expression construct is at least 7 days; whereby said expression construct sensitizes said cancer cell to said chemotherapy, thereby treating said cancer.

Claim 5 is directed to the method of claim 4, wherein said chemotherapy comprises administration of carboplatin.

Claim 7 is directed to the method of claim 5, wherein said radiotherapy is x-rays.

Claim 8 is directed to the method of claim 1, wherein said cancer is head & neck cancer.

Claim 9 is directed to the method of claim 1, wherein said expression construct is a viral expression construct.

Claim 10 is directed to the method of claim 9, wherein said viral expression construct is an adenoviral construct.

Claim 12 is directed to the method of claim 10, wherein said viral expression construct is a replication-defective virus.

Claim 15 is directed to the method of claim 1, wherein said promoter is CMV IE.

Claim 20 is directed to the method of claim 1, wherein the time period between steps (b) and (c) is about 14 days.

Claim 25 is directed to the method of claim 1, wherein recurrence is recurrence at a primary tumor site.

Claim 26 is directed to the method of claim 1, wherein recurrence is recurrence at a metastatic site.

Claim 29 is directed to the method of claim 1, wherein administering in step (b) is intratumoral.

Claim 30 is directed to the method of claim 1, wherein administering in step (c) is intratumoral.

Claim 31 is directed to a method of treating a patient with recurrent cancer, the method comprising administering p53 therapy to the patient, followed by administering a first post-therapy treatment with radio- or chemotherapy at least 7 days thereafter.

Claim interpretations: (I) The chemotherapy drug "carboplatinum" recited in claim 5 is interpreted as "carboplatin" as indicated by Applicant's election of species filed on 10/07/2010, and the spelling of "carboplatin" is consistent with the disclosure by Staar et al. cited in the 103 rejection. (II) Newly added independent claim 31 filed on 06/03/2011 is a genus claim that encompasses the scope of independent claim 1. Independent claim 31 is examined to the extent of elected Group III invention (See further elaboration documented in the Election/Restriction section above in this office action). In this regard, it is worth noting the breadth of "p53 therapy" recited in newly claim 31 encompasses any therapy directly or indirectly linked to the biological function of p53 at nucleic acid and/or protein level, which is much broader than "a nucleic acid segment encoding p53" recited in claim 1.

With regard to the limitation of steps (b) and (c) of claim 1, and the limitations of claims 3, 4, 6, and newly added claim 31, **Roth et al.** (2000) teaches the use of tumor suppressor genes in combination with a DNA damaging agent or factor for use in killing cells, and in particular cancerous cells (See abstract and bridging paragraph, columns 4-5, Roth et al.). A tumor suppressor gene, p53, was delivered via a recombinant *adenovirus*-mediated gene transfer both

in vitro and *in vivo*, in combination with a chemotherapeutic agent (See abstract and lines 25-35 and column 8, Roth et al.). Treated cells underwent apoptosis with specific DNA fragmentation (See abstract and lines 51-61, col. 29, Roth et al.). Direct injection of the p53-adenovirus construct into tumors subcutaneously, *followed by* intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). Roth et al. teaches a method of killing a tumor cell in a tumor of a human cancer patient by expressing functionally active p53 from a DNA construct (claims 1 and 3, Roth et al.), and the expression of p53 results in apoptotic destruction of the tumors (abstract and lines51-53, column 29)

With regard to chemotherapy drug recited in claim 5 and route of administration of p53 construct and chemotherapy drug recited in claims 29 and 30, Roth et al. teaches *direct injection of the p53-adenovirus construct into tumors* subcutaneously, followed by intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). Roth et al. teaches p53 and cisplatin treatment and direct *intratumoral* injection of Ad-p53 (See lines 52-58, column 19, Roth et al., 2000). Roth et al. teaches that DNA damaging agent cisplatin is not absorbed orally and must therefore be delivered via injection intravenously, subcutaneously, *intratumorally* or intraperitoneally (See lines 5-7, column 19).

With regard to the limitation of claim 7, Roth et al. (2000) teaches the treatment method further comprise contacting tumor with DNA damaging agent (claim 42), comprises γ-irradiation, *X-ray*, UV-irradiation (See for instance, line 61 column 4).

With regard to the limitation of cancers recited in claim 8, Roth et al. (2000) teaches the tumors are either malignant or benign and comprise human breast cancer, lung cancer, sarcoma, melanoma, lymphoma, epithelial cancer carcinoma cancer (claims 30-39).

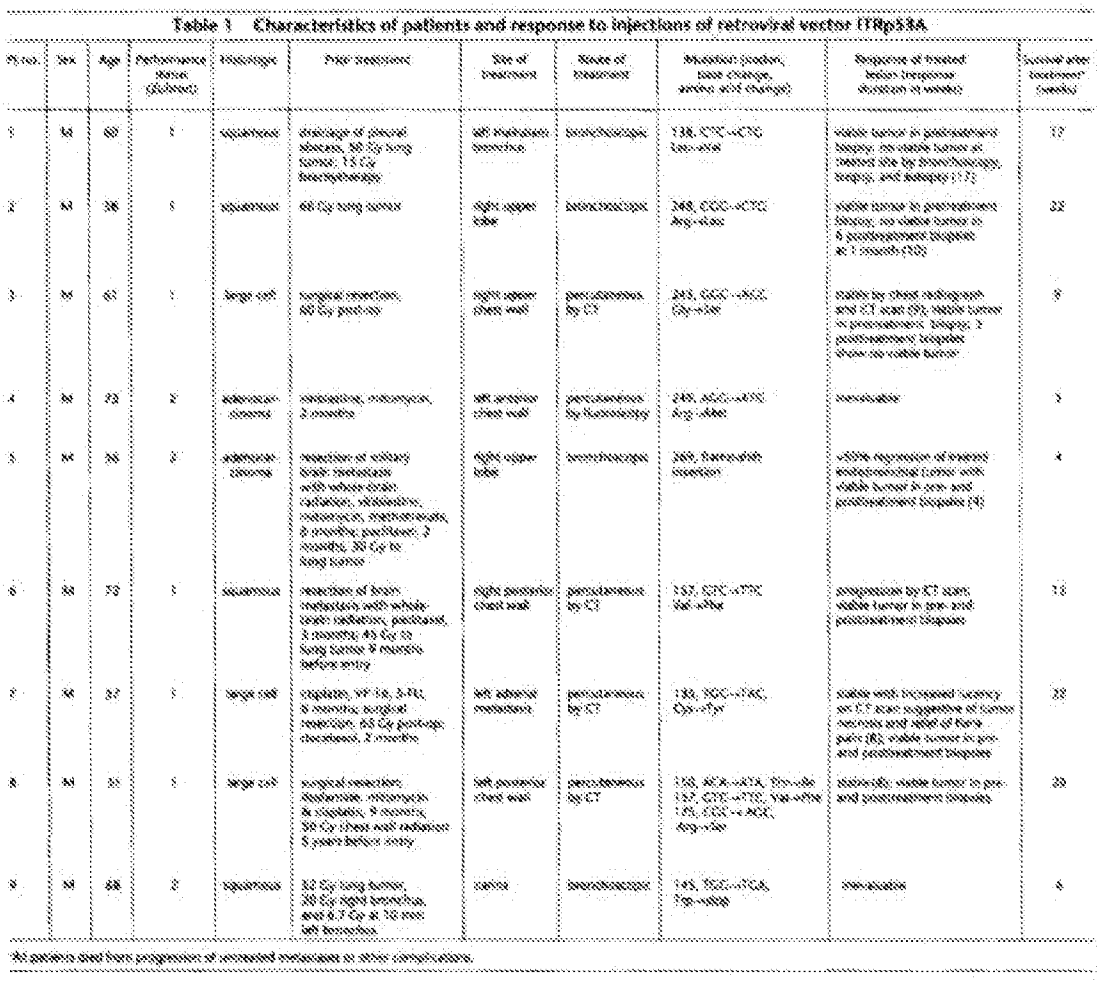
With regard to the limitations of claims 9, 10, 12, and 15, Roth et al. (2000) teaches the expression vector encoding p53 can be delivered by a variety of vectors including adenoviral vectors (claims 23-28, Roth et al.), *replication-deficient* wild-type p53 *adenovirus* (abstract, Roth et al.), adenovirus lacking E1 region (claims 52 and 53), with *CMV IE promoter* driving p53 expression (lines 53-61, column 6, claim 22).

With regard to the limitations of claims 25 and 26, Roth et al. (2000) teaches that p53 has an important role as a determinant of chemosensitivity in human lung cancer cells. A variety of treatment protocols, including surgery, chemotherapy, and radiotherapy, have been tried for human NSCLC, but the long-term survival rate remains unsatisfactory. What is needed is a *combination therapy* that is used alone or as an effective adjuvant treatment to prevent local *recurrence following primary tumor resection* or as a treatment that could be given by intralesional injections in drug-resistant *primary, metastatic*, or locally recurrent lung cancer (See lines 21-30, column 3, Roth et al., 2000).

Roth et al. (2000) does not *explicitly* teach **(I)** step (a) selecting a recurrent cancer patient previously treated with a radiotherapy prior to such recurrence recited in claim 1, **(II)** "carboplatinum" as a chemotherapy drug recited in claim 5, "head and neck cancer" recited in claim 8, and the limitations "wherein the time period between administration of said chemotherapy relative to the administration of said expression construct is at least 7 days recited

in claim 1, and "wherein the time period between steps (b) and (c) is *about* 14 days" recited in claim 20.

(I) With regard to the limitation step (a) selecting a recurrent cancer patient previously treated with a radiotherapy prior to such recurrence recited in claim 1, **Roth et al. (1996)** teaches administration of viral vector containing the wild-type p53 gene into human non-small cell lung cancer. Nine patients *whose conventional treatment failed* were entered into clinical study (See abstract, Roth et al. 1996). Roth et al. teaches *prior treatment* of patient #1 to 9 and responses of treated lesion of these patients (See Table 1, page 986, provided below in this office action, Roth et al., 1996). For instance, the prior treatment of patient #5 include resection of solitary brain metastasis with *whole-brain radiation*, and the response of treated lesion includes >50% regression of treated endobronchial tumor with viable tumor in pre-and post-treatment biopsies.



With regard to **(II)** "carboplatinum" as a chemotherapy drug recited in claim 5, "head and neck cancer" recited in claim 8, **Staar et al.** teaches that radiation therapy (RT) and chemotherapy may be combined in several ways for treating *head-and-neck* cancer. The two treatments may be given simultaneously, *in alteration or* ***sequentially***. RT may be delivered with a conventional fractionation or with an accelerated and/or hyperfractionated regimen. Early randomized trials with conventionally fractionated RT and concurrent single-agent chemotherapy with methotrexate, 5-FU, low-dose cisplatin, or mitomycin C revealed significant improvements in local control and/or survival. *Carboplatin* has radiosensitizing properties

comparable to cisplatin; however, carboplatin can be administered *with minimal hydration, and causes less nausea* (See third paragraph, right column, page 1168, Staar et al., 2001).

With regard to **(II)** the limitations "carboplatinum" as a chemotherapy drug recited in claim 5, "head and neck cancer" recited in claim 8, and the limitations "wherein the time period between administration of said chemotherapy relative to the administration of said expression construct is at least 7 days recited in claim 1, and "wherein the time period between steps (b) and (c) is *about* 14 days" recited in claim 20, **Staar et al.** teaches chemotherapy guidelines as follows: For patients in arm B, *chemotherapy was performed in week one and five. 5-FU was given as continuous infusion* (600 mg/m^2/day) and *carboplatin* as short-term infusion (70 mg/m^2) on *days 1-5 and 29-33*, starting before the first daily fraction. It was recommended to treat these patients on an in-patient basis (See left column, page 1164, Staar et al., 2001). It is noted that the primary reference Roth et al. (2000) teaches the protocol of direct injection of the p53-adenovirus construct into tumors subcutaneously, *followed by* administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). The teachings of Staar et al. regarding 5-FU was given as continuous infusion (600 mg/m^2/day) and administration of *carboplatin* as short-term infusion (70 mg/m^2) on days 1-5 and 29-33 indicates the second administration of chemotherapy being about 14 days (and "at least 7 days" recited in claim 1) after administration of p53 gene. Based on the variation of patients disclosed by Roth et al. (1996) and the time period taught by Staar et al. (2001), the determination of the range of days subsequent to step (b) as recited in step (c) of claim 1 is a process of routine optimization of the protocols for cancer treatment of each patient/subject by the claimed methods. This is in complete agreement of claimed methods

regarding the range of time periods between step (b) and step (c) recited in claim 1 being from "at least 7 days" and up to "about 6 months" (See limitations recited in claims 19-24, with claim 20 reciting "about 14 days" being the elected species among claims 19-24). In this regard, Applicant attention is directed to MPEP 2144.05 cited below.

2144.05 [R-5] Obviousness of Ranges
See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES
A. Optimization Within Prior Art Conditions or Through Routine Experimentation
Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v.

Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Roth et al. (2000) regarding the use of tumor suppressor genes in combination with a DNA damaging agent or factor for use in killing cells, and in particular cancerous cells, and direct injection of the p53-adenovirus construct into tumors subcutaneously, followed by administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors with the teachings of (i) Roth et al. (1996) regarding nine patients whose conventional treatment failed were entered into clinical study, and for instance, the prior treatment of patient #5 include resection of solitary brain metastasis with whole-brain radiation, and the teachings of (ii) Staar et al. regarding guidance of chemotherapy of 5-FU was given as continuous infusion (600 mg/m^2/day) and carboplatin as short-term infusion (70 mg/m^2) on days 1-5 and 29-33, starting before the first daily fraction, and radiation

therapy (RT) and chemotherapy may be combined in several ways for treating head-and-neck cancer as the two treatments may be given simultaneously, in alteration or *sequentially,* to arrive the claimed methods recited in claimed 1, 3-10, 12, 15, 20, 25, 26 and 29- 31 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roth et al. (2000) et al. with the teachings of Roth et al. (1996) and Staar et al. because Roth et al. (2000) teaches the framework of effective treatment of a cancer, for instance treatment of a lung cancer, by p53 gene therapy followed by chemotherapy which for instance uses chemotherapy drug cisplatin, whereas the teachings of Roth et al. (1996) et al. complement the teachings of Roth et al. (2000) by providing detailed characteristics of patients elected for clinical trial of lung cancer treatment by p53 gene therapy. The teachings by Staar et al. (2001) complement the teachings of Roth et al. (2000) by providing the chemotherapy guidelines for treating head and neck cancer using chemotherapy drug carboplatin.

There would have been a reasonable expectation of success given (i) the disclosure of a direct injection of the p53-adenovirus construct into tumors subcutaneously, followed by intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors, by the teachings of Roth et al. (2000) (See abstract and bridging paragraph, columns 7-8, Roth et al. 2000), and (ii) the demonstration of the characteristics of nine patients with lung cancer whose conventional treatment failed were entered into clinical study for lung cancer treatment via a viral vector mediated p53 gene therapy, by the teachings of Roth et al. (1996) (See abstract and Table 1, Roth et al. 1996), and (iii) the demonstration of chemotherapy guidelines regarding chemotherapy of 5-FU was given as continuous infusion

(600 mg/m^2/day) and *carboplatin* as short-term infusion (70 mg/m^2) on days 1-5 and 29-33, for treatment of head and neck cancer, and radiation therapy (RT) and chemotherapy may be combined in sequential order for treating head-and-neck cancer, by the teachings Staar et al. (2001).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and *KSR Guidelines Update* has been published in the Federal Register at 75 *Fed. Reg.* 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Roth et al. (2000), Roth et al. (1996), and Starr et al. (2001) have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments

Applicant argues that the present invention is concerned with the treatment of recurrent cancer and is based on the surprising finding that when recurrent cancer patients in p53 gene therapy trials (typically cancers that had become resistant to conventional treatment) were treated with p53 gene therapy, the p53 gene therapy somehow rendered the recurrent cancer once

again highly amenable to conventional therapy at a future time when the therapeutic gene was no longer being expressed in the tumor. Indeed, very surprising increases in survival relative to historical and treatment controls were seen in these patients. While the underlying mechanisms are unknown, it may be speculated that the p53 therapy somehow reconditioned or reprogrammed the apoptotic pathways of the tumor to make it once again amenable to conventional therapy or the p53 treatment induced apoptosis in subpopulations of tumor cells most resistant to treatment with subsequent outgrowth of tumor cell populations more sensitive to standard therapies. These potential mechanisms are not mutually exclusive and other mechanisms may have contributed to the unexpected findings.

Applicant states that the foregoing observation is entirely distinct from what is described in Roth I - Roth I involves essentially concurrent, combination therapy with p53 and DNA damaging agents, and is based on the finding that essentially co-administration of p53 and DNA damaging agents results in a synergistic or greater than additive apoptotic effect. While Roth I teaches that the co- administration does not have to be at precisely the same time (and their order of administration can be reversed), it does stress the importance of administering within 24 hours of each other in order to achieve the synergistic apoptotic effect:

> Naturally, it is also envisioned that the target cell may be first exposed to the DNA damaging agent(s) and then contacted with a p53 protein or gene, or vice versa. However, in embodiments where the DNA damaging factor and p53 are applied separately to the cell, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell. ***In such instances, it is contemplated that one would contact the cell with both agents within about 12-24 hours of each other, and more preferably within about 6-12 hours of each other, with a delay time of only about 12 hours being most preferred***.

Roth I, col. 4, lines 27-39 (emphasis ours). From the foregoing it is evident that Roth I teaches that the DNA damaging agent and the p53 gene therapy should be administered within 24 hours of each other, thus teaching away from the present invention. Moreover, Roth I only mentions recurrent cancer in passing and says nothing about treatment regimens that have special

efficacy in the case of recurrent disease.

Roth II is similarly irrelevant. Roth II does indicate that patients with recurrent disease were treated with p53 therapy. However, the Action fails to point us to any teaching in Roth II regarding to the effect that such p53 therapy will have promote a longer survival upon further conventional treatment subsequent to the p53 therapy.

Applicants state that we also fail to see the relevancy of Staar, which simply sets forth a conventional chemotherapy regimen, but says nothing about administering conventional therapy following p53 gene therapy in order to dramatically improve survival.

Applicants state that we would note that various claim amendments to claim 1, and new claim 31, have been entered in an attempt to further distance the claimed subject matter from the cited art. For example, both claims now require at least 7 days post-p53 therapy before administration. While it is believed that advantages in accordance with the invention could well be realized with a shorter interval, the amendment here is made for now to distance the present invention from the very different invention of Roth I. Further, we have attempted to craft both main claims to clarify that it is contemplated that the post-p53 conventional therapy is not administered until at the time frame set forth in the claim when the p53 transgene is no longer expressed (i.e., at least 7 days, in the case of claims 1 and 31, and about 14 days in the case of claim 20).

Applicants state that, lastly, the Action's reliance on the "optimization of ranges" doctrine is totally misplaced here. As specifically pointed out in MPEP 2144.05, II, B, the "optimization of ranges" doctrine is only relevant to a recognized "result-effective variable", that is, optimization of an already recognized relationship:

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq, ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not

recognized in the art to be a result- effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

MPEP 2144.05, II. B. Here, the surprising finding that post-gene therapy administration conventional therapy in recurrent cancer can greatly improve survival is totally a novel observation and can in no way be said to constitutes a "result-effective variable" As such, our situation is not unlike that in In re Antonie, mentioned in the above MPEP excerpt, where the court observed that the prior art failed to recognize the relationship between treatment capacity as a function of tank volume to contractor ratio, in holding that the optimization doctrine did not apply.

Response to Applicant's arguments

Roth et al. (2000) certainly discloses multiple embodiments relates to the use of tumor suppressor genes in combination with a DNA damaging agent or factor for use in killing cells, and in particular cancerous cells. The contemplated embodiment "In such instances, it is contemplated that one would contact the cell with both agents within about 12-24 hours of each other, and more preferably within about 6-12 hours of each other, with a delay time of only about 12 hours being most preferred" disclosed by Roth et al. does **not** in any way negate the rest of the embodiments disclosed by Roth et al. (2000) and does **not** in any way invalidate the additional teachings that have been reduced to practice (i.e. the second reference by Roth et al (1996)) . In this regard, it is further noted that ***one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).***

As stated in the maintained rejection, it is noted that the primary reference Roth et al. (2000) teaches the protocol of direct injection of the p53-adenovirus construct into tumors subcutaneously, *followed by* administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). Roth et al. (2000) teaches that p53 has an important role as a determinant of chemosensitivity in human lung cancer cells. A variety of treatment protocols, including

surgery, chemotherapy, and radiotherapy, have been tried for human NSCLC, but the long-term survival rate remains unsatisfactory. What is needed is a *combination therapy* that is used alone or as an effective adjuvant treatment to prevent local *recurrence following primary tumor resection* or as a treatment that could be given by intralesional injections in drug-resistant *primary, metastatic*, or locally recurrent lung cancer (See lines 21-30, column 3, Roth et al., 2000).

The maintained rejection also acknowledges that Roth et al. (2000) does not *explicitly* teach the limitations "wherein the time period between administration of said chemotherapy relative to the administration of said expression construct is at least 7 days recited in claim 1, and "wherein the time period between steps (b) and (c) is *about* 14 days" recited in claim 20.

However, Roth et al. (1996) teaches administration of viral vector containing the wild-type p53 gene into human non-small cell lung cancer. Nine patients *whose conventional treatment failed* were entered into clinical study (See abstract, Roth et al. 1996). Roth et al. teaches *prior treatment* of patient #1 to 9 and responses of treated lesion of these patients (See Table 1, page 986, provided below in this office action, Roth et al., 1996). For instance, the prior treatment of patient #5 include resection of solitary brain metastasis with *whole-brain radiation*, and the response of treated lesion includes >50% regression of treated endobronchial tumor with viable tumor in pre-and post-treatment biopsies.

Furthermore, with regard to the limitation "wherein the time period between administration of said chemotherapy relative to the administration of said expression construct is at least 7 days" recited in claim 1, and "wherein the time period between steps (b) and (c) is *about* 14 days" recited in claim 20, Staar et al. teaches chemotherapy guidelines as follows: For patients in arm B, *chemotherapy was performed in week one and five. 5-FU was given as continuous infusion* (600 mg/m^2/day) and *carboplatin* as short-term infusion (70 mg/m^2) on *days 1-5 and 29-33*, starting before the first daily fraction. It was recommended to treat these patients on an in-patient basis (See left column, page 1164, Staar et al., 2001). It is noted that the primary reference Roth et al. (2000) teaches the protocol of direct injection of the p53-adenovirus construct into tumors subcutaneously, *followed by* administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). The teachings of Staar regarding 5-FU was given as

continuous infusion (600 mg/m^2/day) and administration of *carboplatin* as short-term infusion (70 mg/m^2) on days 1-5 and 29-33 indicates the second administration of chemotherapy being about 14 days (and "at least 7 days" recited in claim 1) after administration of p53 gene. Based on the variation of patients disclosed by Roth et al. (1996) and time period for chemotherapy taught by Staar et al. (2001), the determination of the range of days subsequent to step (b) as recited in step (c) of claim 1 is a process of routine optimization of the protocols for cancer treatment of each patient/subject by the claimed methods. ***This is in complete agreement of claimed methods regarding the range of time periods between step (b) and step (c) recited in claim 1 being from "at least 7 days" and up to "about 6 months" (See limitations recited in claims 19-24, with claim 20 reciting "about 14 days" being the elected species among claims 19-24).*** In this regard, it is worth noting that the specification of instant application provides the following disclosure "The time period between steps (b) and (c) may be ***about 24 hours, about 2 days, about 3 days, about 7 days, about 14 days, about 1 month, about 2 months, about 3 months, or about 6 months***. Recurrence may be recurrence at a primary tumor site or a metastatic site. The subject may have had surgical resection prior to step (b), and/or the method may further comprise surgical resection following step (c)." (See paragraph [0011], US 2008/0293652, publication of instant application). Furthermore, the limitations "about 24 hours", "about 2 days", "about 3 days", "about "3 days" were recited in claims 16-18 filed on 10/07/2010, which were then cancelled on 06/03/2011.

The arguments that "we also fail to see the relevancy of Staar, which simply sets forth a conventional chemotherapy regimen, but says nothing about administering conventional therapy following p53 gene therapy in order to dramatically improve survival" have been fully considered and found **not** persuasive. It is worth noting that Staar et al. is relied on for the teachings regarding the time periods of combined treatment of head-and neck cancer (recited in claim 8 of instant application) with combined radiotherapy and chemotherapy (required by the limitations recited in step (a) and (c) of claim 1). *It is worth noting that the claimed methods do not recite any limitation pertaining to "dramatically improve survival" as Applicant argued.* In this regard, it is noted that the effectiveness of claimed methods of "treating a patient with recurrent cancer" can be broadly evaluated by various assays and/or criteria, which certainly

include decrease in tumor size that has been taught in primary reference Roth et al. (2000) (See for instance Figure 13, lines 11-21, column 13, Roth et al., 2000).

Applicant's arguments that the "optimization of ranges" doctrine is only relevant to a recognized "result-effective variable", that is, optimization of an already recognized relationship have been fully considered and found **not** persuasive. The Examiner maintains the position that based on the variation of patients disclosed by Roth et al. (1996), the determination of the range of days subsequent to step (b) as recited in step (c) of claim 1 is a process of routine optimization of the protocols for cancer treatment of each patient/subject by the claimed methods. This is in complete agreement of claimed methods regarding the range of time periods between step (b) and step (c) recited in claim 1 being from "about 7 days" and up to "about 6 months" (See limitations recited in claims 19-24, with claim 20 reciting "about 14 days" being the elected species among claims 19-24). It is worth noting that the disclosure of "Response of treated lesion (response duration in weeks) in Table 1 of "Characteristics of patients and response to injection of retroviral vector ITRp53A" by Roth et al. (1996) certainly demonstrate the time period of treatment being a "result-effective variable", as stated in MPEP 2144.05, II, B. Similarly, Starr et al. discloses the time period of treatment being a "result-effective variable", in the context of combined treatment of head-and neck cancer (recited in claim 8 of instant application) with combined radiotherapy and chemotherapy (required by the limitations recited in step (a) and (c) of claim1) (See for instance Figures 2-6, pages 1165-1167, Staar et al., 2001)

Conclusion

4. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action (i.e. the rejection of newly added claim 31). Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632